1: Blood 2002 Feb 15;99(4):1314-9

The chimeric anti-CD20 antibody rituximab induces apoptosis in B-cell chronic lymphocytic leukemia cells through a p38 mitogen activated protein-kinase-dependent mechanism.

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Antibodies against CD20 can activate complement and induce antibody-dependent cellular cytotoxicity (ADCC) in B lymphocytes. In B-cell lines, such antibodies also induce apoptosis. In this study, the expression and function of CD20 on B-cell chronic lymphocytic leukemia (B-CLL) cells were analyzed. Flow cytometric analysis demonstrated that B-CLL cells express CD20 with a fluorescence intensity that is significantly weaker than that of normal CD5(+) and CD5(-) B cells and that of malignant CD5(-) low-grade non-Hodgkin lymphoma cells. A small population of cells from healthy donors that have an expression pattern of CD5 and CD20 identical to that of B-CLL cells were identified, and this population was confirmed to be of T lineage, not B lineage. Culture of freshly isolated B-CLL cells in the presence of the chimeric anti-CD20 antibody rituximab and a cross-linking F(ab)(2) fragment, resulted in dose- and time-dependent induction of apoptosis. The induction of apoptosis occurred under conditions in which the influence of complement activation and ADCC was negligible. Cross-linking of rituximab induced strong and sustained phosphorylation of the 3 mitogen activated protein (MAP) kinases c-Jun NH2-terminal protein kinase, extracellular signal-regulated kinase, and p38. Introduction of the p38 inhibitor SB203580 into the system completely blocked signaling downstream of p38, as evidenced by the absence of MAPKAP K2 activity, and significantly reduced the degree of anti-CD20-induced apoptosis. These results demonstrate that cross-linking of rituximab bound to CD20 on freshly isolated B-CLL cells induces apoptosis through a signaling pathway that is dependent on p38 MAP-kinase activation.

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Monoclonal antibody therapies in leukemias.

Tallman MS.

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Significant advances in the development of monoclonal antibodies (unconjugated) and monoclonal antibodies conjugated to potent toxins or cytotoxic agents (immunoconjugates) have enabled improved targeting of leukemic cells with acceptable toxicities. Gemtuzumab ozogamicin, a calicheamicin-conjugated anti-CD33 monoclonal antibody, has demonstrated substantial efficacy in patients with acute myeloid leukemia (AML) and has induced remissions in patients with favorable-, intermediate-, and poor-risk cytogenetics. The immunoconjugate BL-22, comprised of an anti-CD22 monoclonal antibody fused to a fragment of pseudomonas exotoxin PE38, has produced high response rates in patients with purine analog-resistant hairy cell leukemia. Campath-1H (Wellcome, Beckenham, UK, and Ilex Oncology, San Antonio, TX), an anti-CD52 monoclonal antibody, has demonstrated significant activity in patients with previously untreated, relapsed, or refractory chronic lymphocytic leukemia (CLL), as well as in patients with T-cell prolymphocytic leukemia. The anti-CD20 monoclonal antibody rituximab also is effective in treating CLL and is being evaluated in combination with chemotherapeutic agents (cyclophosphamide) and fludarabine. Monoclonal antibodies may sensitize cells to chemotherapy. The optimal role of targeted therapy with monoclonal antibodies and immunoconjugates in acute and chronic leukemias has not yet been determined, but these novel therapies are beginning to fulfill their promise. Semin Hematol 39 (suppl 3):12-19.

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